08/259,321

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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER

18M1/0429

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 2/5/97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or ~~thirty days,~~ whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-3, 5, 7-8, 14-15, 17-21 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-3, 5, 7-8, 14-15, 17-21 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1996-421-632/40206

1. The instant application has been filed under 37 C.F.R. § 129(a).

Claims 1, 3, 14, 17, 20 and 21 have been amended.

Claims 1-3, 5, 7-8, 14-15 and 17-21 are pending.

2. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description of the invention and failing to provide an enabling disclosure without complete evidence either that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of the biological materials.

The specification lacks complete deposit information for the deposit of the hybridoma cell line ATCC No. HB 9892 recited in claims 1, 4 and 20. It is not clear that hybridoma cell lines possessing the identical properties of ATCC No. HB 9892 are known and publicly available or can be reproducibly isolated from nature without undue experimentation. Exact replication of a cell line is an unpredictable event. Although applicant has provided a written description of a method for selecting the claimed hybridoma cell lines and monoclonal antibodies, this method will not necessarily reproduce antibodies and hybridomas which are chemically and structurally

identical to those claimed. It is unclear that one of skill in the art could derive antibodies and hybridomas identical to those claimed. Undue experimentation would be required to screen all of the possible antibody and hybridoma species to obtain the claimed antibodies and hybridomas.

Because one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed in the absence of the availability of the claimed cell line, a suitable deposit for patent purposes, evidence of public availability of the claimed cell line or evidence of the reproducibility without undue experimentation of the claimed cell line, is required.

Applicant's referral to the deposit on page 8 of the specification is an insufficient assurance that all required deposits have been made and all the conditions of 37 CFR 1.801-1.809 met.

If the deposit is made under the provisions of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposit has been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposits will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the provisions of the Budapest Treaty as the Treaty leaves this specific matter to the discretion of each State.

If the deposit is not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability and permanency of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit over his or her signature and registration number averring:

(a) during the pendency of this application, access to the deposits will be afforded to the Commissioner upon request:

(b) all restrictions upon the availability to the public of the deposited biological material will be irrevocably removed upon the granting of a patent on this application:

(c) the deposits will be maintained in a public depository for a period of at least thirty years from the date of deposit or for the enforceable life of the patent of or for a period of five years after the date of the most recent request for the furnishing of a sample of the deposited biological material, whichever is longest; and

(d) the deposits will be replaced if they should become nonviable or non-replicable.

Amendment of the specification to recite the date of deposit and the complete name and address of the depository is required. As an additional means for completing the record, applicant may submit a copy of the contract with the depository for deposit and maintenance of each deposit.

If deposits are made after the effective filing date of the application for patent in the United States, a verified statement is required from a person in a position to corroborate that the cell line described in the specification as filed is the same as that deposited in the depository,

stating that the deposited material is identical to the biological material described in the specification and was in the applicant's possession at the time the application was filed.

Applicant's attention is directed to In re Lundak, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

3. Claims 1-3, 5, 7-8, 14-15, 17-21 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

4. Claims are 1 and 14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The specification, as originally filed, does not provide support for the concept of a first epitope and a second epitope.

5. Claims 1-3, 5, 7-8, 14-15 and 17-21 are rejected under 35 U.S.C. § 112, first paragraph, as failing to provide an adequate written description and enabling disclosure, commensurate in scope with the claims.

Claims 1 and 14 are drawn to antibodies immunoreactive with a first epitope in the activation peptide region in combination with a second epitope consisting of calcium ions. The specification does not adequately teach how to produce the claimed antibody, one which binds to

two different epitopes, one which is in the activation peptide region of Protein C heavy chain and a second which consists of calcium ions. It is conventional knowledge that a give antibody is characterized by the recognition of a single, unique epitope with a unique binding specificity. The specification does not teach how to produce an antibody which binds two distinct epitopes. One of skill in the art would not know how to produce such an antibody absent direction or guidance from the specification. The applicant argues that the HPC-4 antibody is unique in recognizing a combination of a specific peptide and a calcium ion, that in the absence of either the antibody does not bind, and therefore the binding of the HPC-4 antibody is for two epitopes. This is not founds persuasive. The applicant admits that no binding of the HPC-4 antibody is noted in the absence of either of the peptide or the calcium ion. Thus, admittedly, the antibody does not recognize two different determinants. Rather the antibody recognizes a single, unique determinant formed by an interaction of the peptide and the calcium ion.

Claims 2 and 15 are drawn to antibodies comprising peptides selected from the group consisting of amino acid sequences for the CDR regions of the light chain and the heavy chain of the HPC-4 antibody. The disclosure is enabling only for claims limited to antibodies having the functional properties recited in claim 1 wherein the antibodies are characterized as having the heavy chain depicted in Seq ID NO. 10 paired with the light chain depicted in SEQ ID NO. 12, or said sequences minus the signal sequences. It is unpredictable that antibodies comprising only the individual heavy or light chains of the HPC-4 antibody or the heavy and light chains of HPC-4 paired with variable region polypeptides from different antibodies, as encompassed by the

claim will be capable of binding to the activation peptide of protein c in combination with calcium and inhibiting protein C activation by thrombin-thrombomodulin. It is generally accepted by those of skill in the art that properly associated heavy and light chain variable regions are required in order to obtain antigen binding function, in the absence of evidence to the contrary. The record contains no evidence which would allow one of skill in the art to predict that the 4 polypeptides recited in claims 2 and 15 individually possess the functions recited in claims 1 and 14. It appears that undue experimentation would be required to practice the invention as claimed. See M.P.E.P. §§ 706.03(n) and 706.03(z). The applicant argues the applicants do not claim the light chain or heavy chain alone, that they claim only the nucleotide sequences encoding these regions. This is not found persuasive. The claims are broadly drawn to be drawn to antibody fragments that need comprising only one specific peptide sequence selected from the group consisting of the various CDR peptide sequences.

6. Claims 1-3, 5, 7-8, 14-15 and 17-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite in the recitation "immunoreactive." As "immunoreactive" encompasses many different types of immune interactions, the nature of the interaction of the claimed antibody with the antigenic epitope it recognizes is unclear. The applicant is advised to amend the claim to recitation "binds" or "specifically binds."

Claim 1 is vague and indefinite. Is the claim is drawn to a) a recombinant Ca monoclonal antibody or b) antibody fragment comprising the hypervariable region of the monoclonal antibody produced by ATCC No. HB 9892 immunoreactive with a first epitope in the activation peptide region in combination with a second epitope consisting of Ca ions? Or, is the claim drawn to a) a recombinant Ca monoclonal antibody or b) antibody fragment comprising the hypervariable region of the monoclonal antibody produced by ATCC No. HB 9892, both of which are immunoreactive with a first epitope in the activation peptide region in combination with a second epitope consisting of Ca ions?

Claims 1 and 14 are indefinite in the recitation of an antibody which binds to the peptide defined by Seq. ID No. 1 in combination with calcium because the intended meaning is unclear. It is unclear whether the subject antibody binds to an epitope which includes calcium or whether calcium binds to a site on the antibody not involved in epitope recognition.

Claim 4 is vague and indefinite in the recitation of an antibody that contains "human amino acid sequence." The nature of the human sequence, e.g. a human framework, constant region, CDR region, a single amino acid, is not known. Thus, the defining structural characteristics of the antibody and method defined by the claims are not known.

Claim 17 is vague and indefinite in the recitation "human sequence." The nature of the human sequence, e.g. amino acid or nucleotide is not known. The applicant is advised to amend the claim to recite "human amino acid sequences."

"Lable" is misspelled in claim 7.

Claims 7 and 18 are vague and indefinite in the recitations "bound" and "binding." It is unclear if the detectable label is linked or conjugated to the antibody or is "bound" via binding to the antigen binding site of the antibody, i.e. is the antigen target is detectably labeled.

Claims 8 and 19 are confusing in the recitation of an antibody immobilized to a substrate wherein the immobilized antibody is suitable for purification of protein C. It is unclear whether the intended meaning is that substrate to which the antibody is immobilized is one which is suitable for the production of an affinity matrix or whether the suitability of the antibody for purification resides in the inherent properties of the antibody irrespective of the nature of the substrate to which it is bound.

7. The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman*, 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 1-2, 5, 7-8, 14-15 and 20 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 5,202,253. Although the conflicting claims are not identical, they are not patentably distinct from each other because they relate to the same inventive concept. The antibody claimed herein is has the identical properties and variable region amino acid sequences as the HPC-4 monoclonal antibody claimed in U. S. Patent No. 5,202,253. The limitation in instant claim 1, that the subject antibody is "recombinant" and is "expressed in bacterial cells" is given no weight in comparing the claims with those of the '253 patent, since this limitation is deemed to confer no structural difference between the claimed antibody and the prior art antibody. The limitation of claim 20, "having coupled thereto a peptide sequence," is interpreted to be the same as the "enzyme" of claims 3 of U. S. Patent No. 5,202,253.

9. Claims 1-3, 5, 7-8, 14-15 and 17-21 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 of U.S. Patent No. 5,202,253 in view of Morrison or Queen. It would have been obvious to use immunoglobulin gene cloning methods such as those described by Morrison in order to clone the genes encoding the antibody claimed in claims 1-3 of U.S. Patent No. 5,202,253 to produce "recombinant" antibodies that contain human sequences, antibodies containing human amino acid sequences in the constant domain or frame work regions of the variable domain.

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 1-2, 5, 7-8 and 20 are rejected under 35 U.S.C. § 102(b) and (e) as being anticipated by U.S. Patent No. 5,202,253 or U.S. Patent No. 5,147,638. Each of U.S. Patent No. 5,202,253 and U.S. Patent No. 5,147,638 teach monoclonal antibody HPC-4, which inherently possesses the characteristics recited in claims. The limitations in claim 1, that the subject antibody is "recombinant" and "expressed in bacterial cells" are given no weight in comparing the claims with the prior art, since this limitation is deemed to confer no structural difference between the claimed antibody and the prior art antibody. The patentability of a product claim is not governed by the process of production if the process recited in the claim does not alter the identifying characteristics of the product. The burden is shifted to the applicant to establish by comparative evidence that the product taught by the prior art is patentably distinct from that claimed

13. Claims 1-2, 5, 7-8 and 20 are rejected under 35 U.S.C. § 102(b) as being anticipated by D'Angelo et al. (J. Clin. Invest. 77) or Stearns et al. (J. Biol. Chem. 263). Each of D'Angelo et al. and Stearns et al. teach monoclonal antibody HPC-4. The references teach monoclonal antibody HPC-4 coupled to Affigel 10 and coupled to immunobeads (pages 417 and 827, respectively).

14. Claims 1-3, 5, 7-8, 1415 and 17-21 are rejected under 35 U.S.C. § 103 as being unpatentable over any of U.S. Patent No. 5,202,253, U.S. Patent No. 5,147,638, D'Angelo et al. (J. Clin. Invest. 77) or Stearns et al. (J. Biol. Chem. 263) in view of Morrison or Queen.

U.S. Patent No. 5,202,253, U.S. Patent No. 5,147,638, D'Angelo et al. (J. Clin. Invest. 77) and Stearns et al. (J. Biol. Chem. 263) teach monoclonal antibody HPC-4, as previously discussed, above. These references do not teach the production of antibodies by recombinant methodology or the "humanization" of murine monoclonal antibodies by inclusion of human amino acid sequences in the constant and framework regions.

However, both Morrison and Queen teach that methods for immunoglobulin gene cloning and expression were well established in the art at the time the claimed invention was made.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the basic methods taught by Morrison or Queen in order to clone the genes encoding the HPC-4 monoclonal antibody taught by U.S. Patent No. 5,202,253 or U.S. Patent No. 5,147,638, D'Angelo et al. (J. Clin. Invest. 77) and Stearns et al. (J. Biol. Chem. 263). In doing so one of ordinary skill in the art would have obtained antibodies and DNAs encoding antibodies having the structural characteristics of those claimed. One of ordinary skill in the art would have been motivated to produce recombinant antibodies having the variable region of HPC-4 in order to obtain the advantages discussed by Morrison, for example, on page 1207. One would have been motivated to produce chimeric antibodies or humanized antibodies comprising human antibody sequences in view of the art-recognized advantages of reduced immunogenicity in human hosts obtained by replacing rodent antibody sequences with human sequences as discussed by Morrison and Queen.

The applicant admits that there is no argument that the methods used by the applicants (those of Queen and Morrison) were well known in the art. However, the applicant argues that as "the court discussed in In re Deuel, merely having a plan is not enough." That "one skilled in the art simply could not have any basis for determining whether or not an antibody with the unique specificty of HPC-4 could be cloned" and expressed.

This argument has been carefully considered and is not found persuasive. Each case under 35 USC 103 is decided on its own particular basis, each individual case being fact-driven and time-specific. There is nothing intrinsically wrong, in the application of methodology in rejecting product claims under 35 USC 103, depending on the particular facts of the case, the manner and context in which methodology applies, and the overall logic of the rejection. Deuel can not be read as issuing a blanket prohibition against the application of methodology in rejecting product claims defining DNA or cDNA. Furthermore, precedent indicates that it is perfectly acceptable to consider the method by which a compound is made in evaluating the obviousness of the compound. See In re Burt 356 F.2d 115, 119, 148 USPQ 548, 551-552 (CCPA 1966) (in determining obviousness, it is appropriate to consider such matters as (1) the manner of preparation of the compound vis-a-vis the prior art, (2) the structural similarities as well as the differences between the claimed compositions and that of the prior art, and (3) the presence or absence of properties which would be unobvious in view of the prior art). The level of skill in the art of the cloning the genes encoding antibodies was very high at the time of filing of the instant application, the applicant admits as much. The applicant's statement that "one skilled in the art

simply could not have any basis for determining whether or not an antibody with the unique specificty of HPC-4 could be cloned" and expressed is incorrect. While a given monoclonal antibody may have a very unique specificty, this is not an indication that the genes for the antibody will be difficult to clone. Antibodies with very different specificties still share a similar structure in the majority of their residues, and for this reason routine methods have been developed for the cloning of hypervariable regions from any antibody. The possesion of a unique binding specificty in an antibody does not indicate difficuty in determining the nucleotide sequence encoding it. It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to apply the basic methods taught by Morrison or Queen in order to clone the genes encoding the HPC-4 monoclonal antibody taught by U.S. Patent No. 5,202,253 or U.S. Patent No. 5,147,638, D'Angelo and Stearns et al. To obtain the claimed recombinantly produced antibodies.

Additionally, while, In re Deuel affirms the principle that a general method of isolating cDNA or DNA molecules is essentially irrelevant to the question whether the specific molecules themselves would have been obvious, in the absence of prior art that suggests the claimed DNAs, it is pointed out that the instant claims are not drawn to unique species and remain obvious in view of the prior art.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy A. Johnson, Ph.D. whose telephone number is (703) 305-5860. The

examiner can normally be reached on Monday-Friday from 8:30-5:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731. The fax number for the group is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Toni R. Scheiner

TONI R. SCHEINER
PRIMARY EXAMINER
GROUP 1800

Nancy A. Johnson, Ph.D.

April 28, 1997